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Benefits From Small Molecule Administration as Compared With Abciximab Among Patients With ST-Segment Elevation Myocardial Infarction Treated With Primary Angioplasty

A Meta-Analysis

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Objectives The aim of the study was to perform a meta-analysis of randomized trials (RTs) comparing abciximab versus small molecules (eptifibatide and tirofiban) in primary angioplasty (PPCI) for ST-segment elevation myocardial infarction (STEMI).

Background Abciximab has been shown to provide significant benefits in PPCI for STEMI. However, small molecules represent an attractive strategy due to the reversibility of the inhibition of platelet aggregation and the lower costs.

Methods We obtained results from RTs comparing abciximab versus small molecules in PPCI. The literature was scanned by searches of electronic databases (MEDLINE and CENTRAL) up to October 2008. The following key words were used: RT, myocardial infarction, reperfusion, primary angioplasty, glycoprotein IIb/IIIa inhibitors, abciximab, tirofiban, and eptifibatide. Concerning tirofiban, we only included trials or groups of patients with high-dose bolus and infusion. The primary end point was 30-day mortality. Secondary end points were 30-day reinfarction, post-procedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3, and ST-segment resolution.

Results A total of 6 RTs were included in the meta-analysis, involving 2,197 patients (1,082 randomized to abciximab and 1,115 to small molecules [high-dose tirofiban in 5 trials and eptifibatide in 1 trial]). Abciximab did not improve post-procedural TIMI flow grade 3 (89.8% vs. 89.1%, $p = 0.72$) or ST-segment resolution (67.8% vs. 68.2%, $p = 0.66$). Abciximab did not reduce 30-day mortality (2.2% vs. 2.0%, $p = 0.66$) or reinfarction (1.2% vs. 1.2%, $p = 0.88$), nor was there any difference in major bleeding complications (1.3% vs. 1.9%, $p = 0.27$).

Conclusions This meta-analysis shows among STEMI patients undergoing PPCI similar results between abciximab and small molecules in terms of angiographic, electrocardiographic, and clinical outcome. (J Am Coll Cardiol 2009;53:1668–73) © 2009 by the American College of Cardiology Foundation

Primary angioplasty has been shown to reduce mortality as compared with thrombolysis, due to the ability to restore Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 more rapidly in the vast majority of patients (1). However, suboptimal reperfusion may be observed in a relatively large proportion of patients despite TIMI flow grade 3, mainly due to no-reflow phenomenon and distal embolization (2). Large interest has been focused in the last years on the adjunctive administration of glycoprotein (GP) IIb/IIIa inhibitors to improve perfusion and mortality. Previous meta-analyses of randomized trials (3,4) have shown significant benefits in mortality and reinfarction with abciximab administration as compared with placebo. However, growing interests have been observed on the role of small molecules (eptifibatide and tirofiban). In fact, due to the reversibility of the inhibition of platelet aggregation and the lower costs, they represent a very attractive strategy. Several randomized trials have so far been conducted, but all of them were underpowered to detect any difference in terms of hard clinical end points such as death and reinfarction. Thus, the aim of the current study was to perform a meta-analysis of randomized trials to evaluate whether abciximab may offer benefits in mortality as compared

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with small molecules among ST-segment elevation myocardial infarction (STEMI) patients undergoing primary angioplasty.

Methods

Eligibility and search strategy. We obtained results from all randomized trials evaluating the benefits of adjunctive GP IIb/IIIa inhibitors among STEMI patients undergoing primary angioplasty. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL), the scientific session abstracts in *Circulation*, *Journal of the American College of Cardiology*, *European Heart Journal*, and *American Journal of Cardiology* from January 1990 to October 2008. Furthermore, oral presentations and/or expert slide presentations were included (searched on the TCT, EuroPCR, ACC, AHA, and ESC websites from January 2002 to October 2008). The following key words were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, GP IIb/IIIa inhibitors, abciximab, tirofiban, and eptifibatide.

Inclusion criteria were: randomized treatment allocation and availability of complete clinical data. Exclusion criteria were: follow-up data in less than 90% of patients and ongoing studies or irretrievable data. No language restrictions were enforced.

Data extraction and validity assessment. Data were independently abstracted by 2 investigators. In case of incomplete or unclear data, authors, where possible, were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

Outcome. Primary end point was 30-day mortality. Secondary end points were reinfarction at 30 days, post-procedural TIMI flow grade 3 and ST-segment resolution. Major bleeding complications were assessed as safety end point.

Data analysis. Statistical analysis was performed using the Review Manager 4.27 and SPSS 11.0 statistical package (SPSS Inc., Chicago, Illinois). Odds ratio (OR) and 95% confidence intervals (CIs) were used as summary statistics. The pooled OR was calculated by using a fixed-effect model with the Mantel-Haenszel method. The DerSimonian and Laird random effect models were additionally applied to calculate pooled OR in case of significant heterogeneity across studies. Between-study heterogeneity was analyzed by means of: $I^2 = [(Q - df)/Q] \times 100\%$, where Q is the chi-square statistic, and df is its degrees of freedom. The potential publication bias was examined by constructing a "funnel plot," in which the standard error of the ln OR was plotted against the OR (30-day mortality). The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUORUM) guidelines (5).

Results

Eligible studies. Of the 865 potentially relevant articles initially screened, a total of 7 trials were initially identified (6–12). One trial was excluded because no data were available on clinical outcome (the first author was contacted) (9). Thus, a total of 6 trials were finally included in the meta-analysis (Fig. 1), involving 2,197 patients (1,082 or 49.2% randomized to abciximab and 1,115 or 50.8% randomized to small molecules). Characteristics of the included trials are shown in Table 1. No disagreement was observed in data collection. In the STRATEGY (Tirofiban and Sirolimus-Eluting Stent vs Abciximab and Bare-Metal Stent for Acute Myocardial Infarction: A Randomized Trial) (8) and MULTISTRATEGY (Multicentre Evaluation of Single High-Dose Bolus Tirofiban vs Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction) (10) trials, patients were additionally randomized to bare-metal stents and sirolimus-eluting stents. High-dose tirofiban was used in 5 studies (6–8,10,11), whereas eptifibatide was tested in the EVA-AMI (Eptifibatide Versus Abciximab in Primary PCI for Acute ST elevation Myocardial Infarction) trial (12). In the study by Ernst et al. (6), patients were randomized to placebo, abciximab, high-dose tirofiban, and tirofiban at standard dose, but only abciximab and high-dose tirofiban patients were included in our study.

Abbreviations and Acronyms

CI = confidence interval
GP = glycoprotein
OR = odds ratio
p_{het} = p heterogeneity
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction

Clinical end points. As shown in Figure 2, abciximab did not reduce either 30-day mortality (2.2% vs. 2.0%, OR: 1.14, 95% CI: 0.64 to 2.04, p = 0.66, p heterogeneity [p_{het}] = 0.62) or reinfarction (1.2% vs. 1.2%, OR: 0.94, 95% CI: 0.44 to 2.04, p = 0.88, p_{het} = 0.2), as compared with small molecules. As shown in Figure 3, no publication bias was observed.

Angiographic and electrocardiographic end points. As shown in Figure 4, abciximab did not improve either post-procedural TIMI flow grade 3 (89.8% vs. 89.1%, OR: 1.03, 95% CI: 0.78 to 1.36, p = 0.72, p_{het} = 0.62) or ST-segment

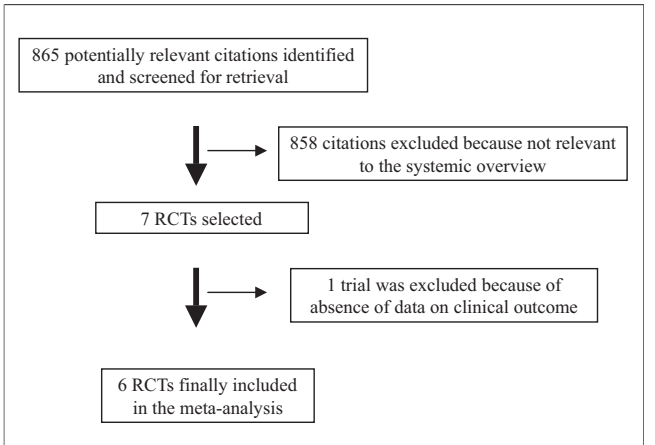

Figure 1 Flow Diagram of the Systematic Overview Process

RCT = randomized controlled trial.

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Table 1 Characteristics of Randomized Trials Included in the Meta-Analysis

Study (Ref. #)	Period	N	Administration of Study Drug	Study Drug Design (Number of Patients)	Primary End Point	Definition of Major Bleeding Complications
Ernst et al. (6)	2002–2003	59	Peri-procedural	Abciximab (n = 30) or high-dose tirofiban (n = 29)	Platelet aggregation inhibition	Blood transfusion or surgery, intracranial or peritoneal hemorrhage
Danzi et al. (7)	2002	100	Peri-procedural	Abciximab (n = 50) vs. high-dose tirofiban (n = 50)	Wall motion score index	NA
MULTISTRATEGY (10)	2004–2007	744	Pre-procedural	Abciximab-SES (n = 186), abciximab-BMS (n = 186), high-dose tirofiban-SES (n = 186), high-dose tirofiban-BMS (n = 186)	ST-segment resolution	TIMI major bleeding
STRATEGY (8)	2003–2004	175	Pre-procedural	Abciximab-BMS (n = 88) vs. high-dose tirofiban-SES (n = 87)	8-month combined death, reinfarction, stroke, and binary restenosis	TIMI major bleeding
FATA (11)	2005–2007	692	Pre- and peri-procedural	Abciximab (n = 341) vs. high-dose tirofiban (n = 351)	ST-segment resolution	Intracranial hemorrhage, bleeding requiring surgery or transfusion, Hb drop >5 g/l
EVA-AMI (12)	2006–2007	429	Peri-procedural	Abciximab (n = 203) vs. eptifibatide (n = 226)	ST-segment resolution	NA

Abciximab dose: 0.25 mg/kg intravenous bolus followed by 12-h infusion at 0.125 mg kg^{-1} min^{-1}; eptifibatide dose: 2 boluses of 180 mg/kg intravenous 10 min apart, then 2.0 mg kg^{-1} min^{-1} infusion; high-dose tirofiban: 25 μg/kg bolus and 0.15 μg/kg/min infusion over 18 to 24 h.

BMS = bare-metal stent(s); EVA-AMI = Eptifibatide Versus Abciximab in Primary PCI for Acute ST elevation Myocardial Infarction trial; FATA = Facilitated Angioplasty with Tirofiban or Abciximab trial; Hb = hemoglobin; MULTISTRATEGY = Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction study; NA = not available; Pre-procedural = before stent insertion; Peri-procedural = after initial angiography; SES = sirolimus-eluting stent(s); STRATEGY = Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent for Acute Myocardial Infarction: A Randomized Trial; TIMI = Thrombolysis In Myocardial Infarction.

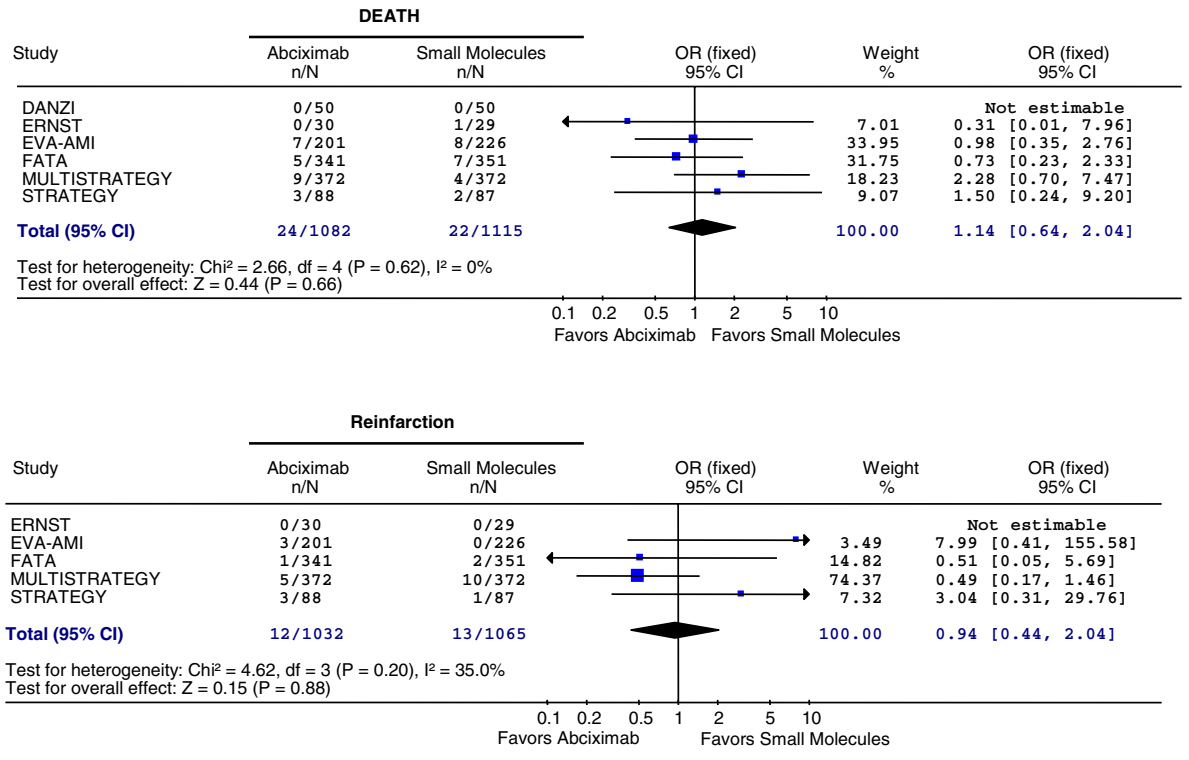

Figure 2 Clinical Outcome

Comparison between abciximab and small molecules in terms of mortality **(top)** and reinfarction **(bottom)** at 30-day follow-up, with odds ratios (ORs) and 95% confidence intervals (CIs). The size of the data markers **(squares)** is approximately proportional to the statistical weight of each trial. EVA-AMI = Eptifibatide Versus Abciximab in Primary PCI for Acute ST elevation Myocardial Infarction trial; FATA = Facilitated Angioplasty with Tirofiban or Abciximab trial; MULTISTRATEGY = Multicentre Evaluation of Single High-Dose Bolus Tirofiban Versus Abciximab With Sirolimus-Eluting Stent or Bare Metal Stent in Acute Myocardial Infarction study; STRATEGY = Tirofiban and Sirolimus-Eluting Stent Versus Abciximab and Bare-Metal Stent for Acute Myocardial Infarction: A Randomized Trial.

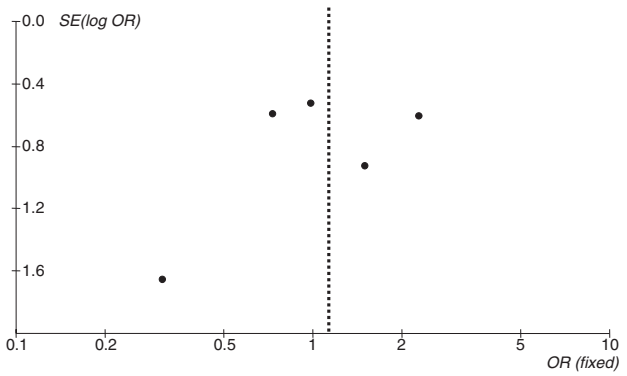

Figure 3 **Funnel Plot of All Studies Included in the Meta-Analysis**

The standard error (SE) of the ln odds ratio (OR) was plotted against the OR for mortality. No skewed distribution was observed, suggesting no publication bias. The study by Danzi et al. (7) is not represented due to the absence of death at follow-up in both groups.

resolution (67.8% vs. 68.2%, OR: 0.96, 95% CI: 0.78 to 1.17, p = 0.66, p_{het} = 0.3), as compared with small molecules.

Bleeding complications. As shown in Figure 5, abciximab was associated with slightly lower rates of major bleeding complications (1.3% vs. 1.9%, OR: 0.69, 95% CI: 0.36 to 1.34, p = 0.27, p_{het} = 0.44).

Discussion

The main finding of this meta-analysis is that abciximab does not provide significant benefits in post-procedural TIMI flow grade 3, post-procedural ST-segment resolution, mortality, and reinfarction at 30 days follow-up, with slightly lower rates of major bleeding complications as compared with small molecules.

Several randomized trials have shown that primary angioplasty is superior to thrombolysis. However, although primary angioplasty is able to restore TIMI flow grade 3 in the vast majority of patients, a relatively large proportion of patients experience poor reperfusion (2). In the last years, growing interests have been focused on the role of distal embolization as a major determinant of poor reperfusion (2). GP IIb/IIIa inhibitors are the most powerful class of antiplatelet therapies. A recent meta-analysis has shown significant benefits in mortality and reinfarction with adjunctive abciximab administration (3). The benefits in mortality have been confirmed at long-term follow-up (4). However, larger interests have been focused in the last years on the role of small molecules (eptifibatide and tirofiban). In

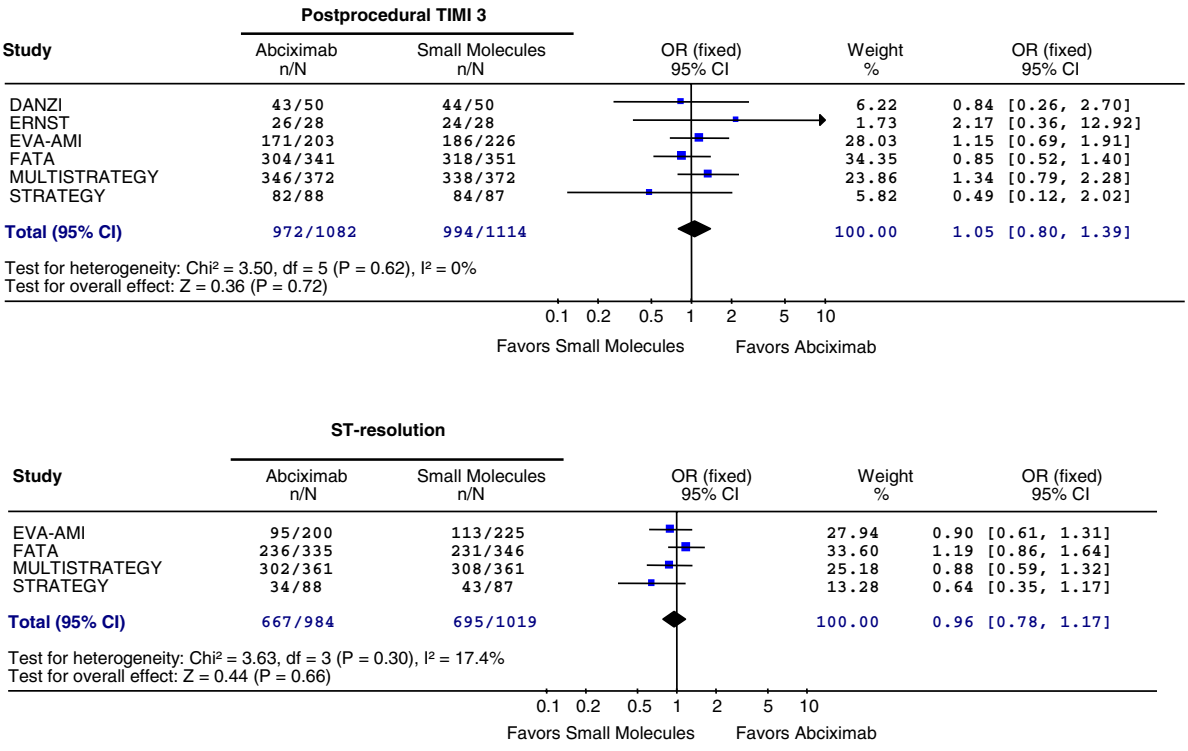

Figure 4 **TIMI Flow Grade 3 and ST-Segment Resolution**

Comparison between abciximab and small molecules in terms of post-procedural Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 **(top)** and complete ST-segment resolution **(bottom)**, with ORs and 95% CIs. The size of the data markers **(squares)** is approximately proportional to the statistical weight of each trial. Complete ST-segment resolution was defined as ST-segment resolution >70%, except in the MULTISTRATEGY trial, where a threshold of 50% was used. Abbreviations as in Figure 2.

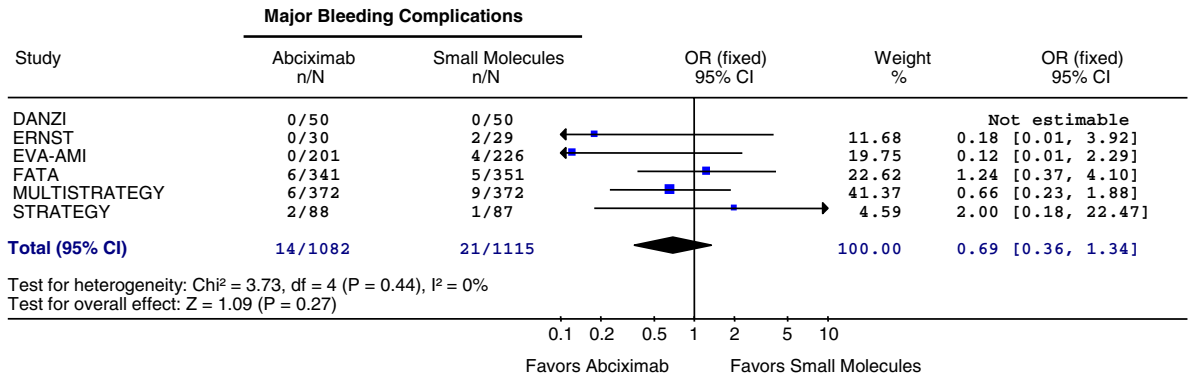

Figure 5 Major Bleeding Complications

Comparison between abciximab and small molecules in terms of major bleeding complications, with ORs and 95% CIs.
The size of the data markers **(squares)** is approximately proportional to the statistical weight of each trial. Abbreviations as in Figure 2.

fact, even though the antiplatelet effects of abciximab may be reversed by platelet infusion, small molecules represent a very attractive strategy due to the reversibility of the inhibition of platelet aggregation at the end of the infusion and the lower costs. A previous large trial in elective or urgent percutaneous coronary angioplasty comparing abciximab and standard dose of tirofiban has shown a significant difference in clinical outcome at 30-day but not 180-day follow-up (13,14). However, in small randomized trials (6,8), it was shown that high-dose tirofiban was associated with a better platelet inhibition as compared with abciximab. Several randomized trials have compared abciximab to high-dose tirofiban or eptifibatide in STEMI patients undergoing primary angioplasty (6–8,10,11). The first trial was conducted by Danzi et al. (7), who in a small cohort of patients did not observe any difference in clinical outcome and in left ventricular functional recovery. In the STRATEGY (8) and MULTISTRATEGY (10) trials, no difference in death and/or reinfarction was observed between high-dose tirofiban and abciximab. In the EVA-AMI trial (12), 400 STEMI patients were randomly assigned to periprocedural administration of eptifibatide or abciximab, with similar outcome observed between the 2 molecules. The major limitation of the study is that the primary end point (ST-segment resolution at 60 to 90 min) was available in only 50% of patients. Even though the recent FATA (Facilitated Angioplasty with Tirofiban or Abciximab) trial failed to show noninferiority of tirofiban versus abciximab, the authors found a similar clinical outcome between the 2 groups of patients (11).

In our meta-analysis, including 2,197 patients, we did not observe any difference in clinical outcome between abciximab and small molecules. According to current costs of treatment with GP IIb/IIIa inhibitors (abciximab = 1,542€; tirofiban = 358€; eptifibatide = 195€), we would save a total of 1,184.00€ and 1,347.00€ per each patient treated with tirofiban or eptifibatide, respectively, as compared with abciximab. Future large randomized trials are certainly needed to compare abciximab versus small molecules in high-risk STEMI patients. In fact, in a previous analysis, we observed a significant relationship between risk profile and benefits from abciximab administration (15).

Study limitations. The availability of individual patients' data would have further improved the results of our meta-analysis. We analyzed short-term outcomes, whereas some GP IIb/IIIa inhibitor studies have demonstrated increased survival benefits with longer follow-up (4). Furthermore, if we would consider as clinically relevant a reduction in mortality of 1% from the mortality (2%) observed with small molecules, with a statistical power of 80% and significance level (alpha) of 0.05, a total of 2,514 patients per group would have been needed to show such a difference. Thus, our study population and analysis was statistically underpowered (60%). Data on the interval between administration of the drug and PCI were not available from many trials. However, in the vast majority of them, GP IIb/IIIa inhibitors were started after initial angiography, and thus with a presumably very short interval between administration of the drug and percutaneous coronary intervention. Finally, the limits in the evaluation and interpretation of publication bias due to the restricted number of randomized trials included in our meta-analysis must be recognized.

Conclusions

This meta-analysis shows among STEMI patients undergoing primary angioplasty similar results between abciximab and small molecules in terms of angiographic, electrocardiographic, and clinical outcome.

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Key Words: primary angioplasty ■ meta-analysis ■ abciximab ■ STEMI ■ small molecules.